CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

NALED

SB 950-041, Tolerance #00215
Chemical Code: 418

August 3, 1987
Revised 1/21/88, 10/12/88, 5/24/89, 2/7/91, 8/25/94, 11/8/94, 1/9/96

DATA GAP STATUS

Chronic rat:	(See "Combined rat", below).
Chronic dog:	No data gap, possible adverse effect.
Combined rat:	No data gap, possible adverse effect.
Oncogenicity mouse:	No data gap, no adverse effect.
Reproduction rat:	No data gap, possible adverse effect.
Teratology rat:	No data gap, no adverse effect.
Teratology rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.

Chromosomal aberration: No data gap, no adverse effect.

DNA damage: No data gap, no adverse effect.

Neurotoxicity: No data gap, no adverse effect1

---

1 - Studies in both rat & hen.

Toxicology One-liners are attached: "**" indicates an acceptable study, "**Bold face**" of volume/record number indicates a possible adverse effect.

Revised by F. Martz, 1/21/88; Kishiyama, Parker, Gee, 10/12/88; Kishiyama, Gee, 5/24/89; Silva, 2/7/91, 7/27/94, 11/8/94, 1/9/96.

See "Guidance for the Reregistration of Pesticide Products Containing NALED as the Active Ingredient", US EPA, 6/83. EPA 1-liners dated 1985. Gee, 5/24/89.

Rectified with Library printout through record #: 131952 & in volume #: 215-143.
FILE Name: T960109

II. TOXICOLOGY ONE-LINERS

COMBINED CHRONIC FEEDING/CARCINOGENICITY RAT

** **064-071 037591-98** (With rebuttal and supplemental information in 098 064051): "Dibrom Chronic Oral Toxicity/Carcinogenicity Study in Rats," (Bio-Research Laboratories, 6/7/84). Naled, purity approximately 92%, administered by gavage to 55 Sprague-Dawley rats/sex/dose at 0, 0.2, 2.0, 10.0 mg/kg/day. **ADVERSE EFFECT**: mammary adenocarcinomas in males, LEL = 2.0 mg/kg/day. Other effects: cholinesterase inhibition in brain, plasma and RBC, NOEL = 0.2 mg/kg/day. Initially unacceptable, insufficient information for assessment (J. Wong, 3/28/85). Again unacceptable, lacked dose level justification (C. Aldous, 1/24/86). This was satisfied by first rebuttal, but still unacceptable. A review (F. Martz, 8/3/87) revealed an oncogenic adverse effect (male mammary tumors) and the need for historical tumor incidence for male mammary adenocarcinomas. Now ACCEPTABLE with historical control data supplied in 064051 (F. Martz, 1/21/88).

EPA One-Liner (1985): Oncogenic NOEL > 10 mg/kg/day (HDT); systemic NOEL > 10 mg/kg/day; ChE NOEL = 0.2 mg/kg/day; Levels of 10 mg/kg/day showed slight RBC ChE inhibition, moderate plasma and brain ChE inhibition. Core Grade = supplementary, minimum.

097 064701, "Addendum to Lifetime Study in Rats with CHEVRON Naled Technical (SX-1278)", (Bio-Research Laboratories Project No. 9394, Ortho Test no. S-1802, May 24, 1983). Dosage formulation analysis indicate that the dosage formulations were homogeneous and stable during the time required to dose animals. Assays of Dibrom technical (93.3% pure) indicate stability when stored in a freezer, but unstable at ambient temperatures. This addendum provides useful information for an ACCEPTABLE study (064-071, 037591-98). (JSK & J. Parker, 10/07/88).

043 022768. Exact duplicate of #037591 above.

032 928896. SBCS31275E, rebuttal to combined rat study, record #037591-98 above; Prior review of report (C. Aldous, 1/24/86) found the lack of dose level justification to be the major deficiency. Rebuttal cites pilot study results and steep dose-response curve for naled, satisfying this criticism. (F. Martz, 5/22/87).

098 064051: Second rebuttal (1/6/88) to record #037591-98 above: provided historical control data as requested. Upgraded study to acceptable with adverse effect. (F. Martz, 1/21/88).

033 928918: Interim report of study with record number 037591-98.

CHRONIC TOXICITY DOG

** **087 046846-046847**, "One-Year Chronic Oral Toxicity Study in Dogs With Naled Technical", (IRDC, report no: 415-044, 6/10/86). Naled technical, 91.4% pure, by oral gavage at 0, 0.2, 2.0 and 20.0 mg/kg/day to 6 dogs/sex/level for one year; mild testicular degeneration, focal mineralization of spinal cord, anemia, and mild splenic siderosis; plasma, RBC and brain cholinesterase inhibition; overall NOEL = 0.2 mg/kg/day. Originally reviewed as unacceptable, needing dose level justification (G. Patterson, 11/7/86); review of supplemental data by F. Martz (5/22/87) changed status to complete and ACCEPTABLE with a possible adverse effect (testicular degeneration, focal mineralization of the spinal cord and mild splenic siderosis).

EPA One-Liner not available.

092 055451: "A Four-Week Dibrom Oral Toxicity Study in Dogs", Bio-Research Laboratories, 1/10/87; Supplemental to #046846-7 above, upgraded study status to ACCEPTABLE. (F. Martz, 5/22/87).

ONCOGENICITY MOUSE

** 044 026887-026886, "Lifetime Oral Carcinogenicity Study in Mice", (IRDC, 3/19/84). Naled, 92.7% pure, at 0, 3, 15, 75/50 mg/kg/day by gavage to 60 mice/sex/group for 89 weeks; high dose reduced to 50 mg/kg at 27 weeks due to mortality (i.e. 75 mg/kg > MTD); interim sacrifice of 10 mice/sex/group at 52 weeks; oncogenic NOEL > 75/50 mg/kg/day, toxic NOEL = 15 mg/kg/day, based on mortality at 75 mg/kg/day; ACCEPTABLE. (J. Wong, 4/1/85 ; F. Martz, 7/15/87).

EPA One-Liner: Oncogenic NOEL > 75/50 mg/kg/day; Systemic NOEL = 15 mg/kg/day. Core Grade = supplementary, minimum.

REPRODUCTION RAT

** **051 027114 (plus record #s 034059-034065 in volumes 057-061)**, "Two-Generation Reproduction Study in Rats With Dibrom," (Bio/dynamics, 3/22/85). Naled, 91.0% pure, by oral gavage in 0.5% CMC at 0, 2, 6 or 18 mg/kg/day to 15 male and 30 female CD rats/level for two-generations; decreased pup survival and body weights in F_{2b} only at 18 mg/kg; reduced number of pups at birth at 6 & 18 mg/kg in F_{2b} only; reproductive NOEL = 2 mg/kg, no parental NOEL (decreased body weight gain in all treated male groups). Complete and ACCEPTABLE. (Gee, 9/9/85).

EPA One-Liner not available.

018 046120. Summary, Dibrom Residue Tolerance Petition Reproduction Study 3-Generation - Rat. Summary (1 page) reports no abnormalities to 3rd generation parents or litters observed with Dibrom up to and including 25 ppm. No worksheet or formal review. This study is not on file at CDFA and should be submitted. (Kishiyama, 5/23/89 and Gee, 5/24/89).

TERATOGENICITY RAT

** 073 037600, "Teratology Study in Rats With Naled Technical," (Science Applications, Inc., 1/18/84). Naled Technical, 91.4% pure, by oral gavage in CMC at 0, 2, 10 and 40 mg/kg/day to 30 CD rats/level days 6-19 (plug=day 0); maternal NOEL = 10 mg/kg/day (cholinergic symptoms

and slight but significant decrease in body weight gain at 40 mg/kg during the dosing period); developmental NOEL = 40 mg/kg/day (HDT). Complete and ACCEPTABLE. (C. Aldous, 1/17/86).

EPA One-Liner: Teratogenic NOEL > 40 mg/kg/day (HDT), Fetotoxic NOEL > 40 mg/kg/day, Maternal NOEL = 10 mg/kg/day, Core Grade = Minimum

038 000892. Partial duplicate (21 pp.) of 037600 above.

025 023505, "Teratologic Assessment of Maleic Hydrazide and Daminozide, and Formulations of Ethoxyquin, Thiabendazole and Naled in Rats," (publication in J. Environ. Sci. Health, B14(6): 563-577, 1979). Fly Killer D, 36% naled, in corn oil by oral gavage, at 100, 50, 25, or 0 mg/kg/day, unspecified whether expressed as AI or formulated material, to 15-19 pregnant Wistar rats/group; no adverse effects reported. UNACCEPTABLE, not upgradeable, insufficient information for assessment. (F. Martz, 7/29/87).

TERATOGENICITY RABBIT

** 072 037599, "Teratology Study in Rabbits With Chevron Naled Technical," (Chevron Environmental Health Center, 2/28/85). Naled technical,92.5% pure, by oral gavage in 0.5% CMC at 0, 0.2, 2 or 8 mg/kg/day to 20 rabbits/level; no adverse effects; maternal NOEL = developmental NOEL = 8 mg/kg/day (highest dose tested); originally reviewed by C. Aldous (1/16/86) as unacceptable, needing justification of dosage levels. Upgraded to ACCEPTABLE by F. Martz, 5/22/87, upon review of rebuttal (SBCS131275E) and range-finding study (034058) cited below.

EPA One-Liner not available.

056 034058, "Pilot Teratology Study in Rabbits With Chevron Naled Technical (SX-1397)", (SOCAL 2194, Chevron Environmental Health Center, 1/24/85; supplemental to #037599 above). Maternal toxicity at 10 mg/kg, lowest dose tested.
Supplemental information upgraded rabbit teratology study, #037599, to ACCEPTABLE. (F. Martz, 5/22/87).

050 026891: partial duplicate of 037599.

034 928919: "Teratogenic Study With Naled Technical in Albino Rabbits," IBT, 3 pp.--Invalid.

GENE MUTATION

** 105 072239 "Microbial/Mammalian Microsome Plate Incorporation Mutagenicity Assay with Naled Technical (SX-1665)." (Chevron Environmental Health Center , Inc., July 18, 1988, J. Carver) Naled, 93.3%; tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 with and without rat liver activation (Aroclor induced); First trial: 0 (DMSO), 0.003, 0.1, 0.33, 0.1 or 0.33 mg/plate, second trial at 0, 0.01, 0.33, 0.1, 0.33 or 1.0 mg/plate; also used E. coli strain WP2 uvrA; triplicate plates each trial; plate incorporation assay; although some colony counts were statistically significant, there were no reproducible results and none were twice the spontaneous rate; no evidence of an adverse effect; ACCEPTABLE with minor variances. (Kishiyama, Gee, 5/24/89)

042 022776, "Further Mutagenicity Studies on Pesticides in Bacterial Reversion Assay Systems," (publication in Mutation Research, 116: 185-216, 1983 - Literature review of Ames assays performed on 228 pesticides). Insufficient information for adverse effects assessment; Brief Summary, results reported as "-" UNACCEPTABLE, not upgradeable. (J. Wong, 3/28/85).

EPA One-Liner: No specific data on Naled provided; Core Grade = Unacceptable.

042 035744 "Activity of Organophosphorus Insecticides in Bacterial Tests for Mutagenicity and DNA Repair--Direct Alkylation Versus Metabolic Activation and Breakdown. II. O-O-Dimethyl-0-(1,2-dibromo-2,2-dichloroethyl)-phosphate and two O-Ether Derivations of Trichlorfon," (publication in Chem.-Biol. Interactions, 43: 361-370, 1983). Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 with and without activation (male mice) tested; 0.1 and 0.3 ml S9 per ml mix tested; mutagenicity in TA100 claimed, but reversion rate < 2x background - a result usually considered equivocal for TA100. revertants appeared to be greater in number with 0.3 than 0.1 but data by graph only. UNACCEPTABLE, not upgradeable. (J. Wong, 3/28/85 and Gee, 5/23/89).

EPA One-Liner: Positive with/without mouse MA in TA100 (Ames); Core Grade = Acceptable.

042 035745, "Mutagenicity of Organophosphorus Compounds in Bacteria and Drosophila," (publication in Mutation Research, 28: 405-420, 1975). S. typhimurium (11 strains) tested; mutagenicity in tester strain TA1535 was claimed, but insufficient information for independent assessment. UNACCEPTABLE, not upgradeable. (J. Wong, 3/18/85).

EPA One-Liner: Reported positive in S. typhimurium strain TA 1535 of 11 bacterial strains tested; Core Grade = NOT ACCEPTABLE.

042, 022774, "Mutagenicity of Pesticides in the Salmonella/Microsome System", (Kor. Jour. Microbiol. Vol. 14, 123-134, 1976 - journal article; abstract and tables in English, remainder untranslated; S. typhimurium (strains TA98, TA100, TA1535 and TA1538); "ambiguous" mutagenicity in strains TA1535 and TA100 reported and negative results with TA1538 and TA98, but insufficient information present for independent assessment; Incomplete (missing detailed protocol information and results in English); UNACCEPTABLE, not upgradeable. (J. Wong, 3/28/85 and Gee, 5/23/89).

EPA One-Liner: Reported negative in S. typhimurium strain TA 100; Core Grade = NOT Acceptable.

045 014823, "Pesticide Mutagenicity in Bacillus subtilis and Salmonella typhimurium Detectors," (publication in J. Agric. Food Chem., 29: 268-271, 1981). Naled (no purity information); S. typhimurium (strains TA1535, TA1536, TA1537, TA1538, TA98, and TA100) and B. subtilis (strains TKJ5211 & 6321), with and without rat liver activation; 50, 100 or 300 µg/plate by spot test, 0 to 50 µg/plate with 30 minutes preincubation; mutagenicity indicated in S. typhimurium strains TA1535 and TA100 and in B. subtilis strains TKJ5211 and TKJ6321, but insufficient information presented for independent adverse effects assessment; data presented as "+" or graph only; Incomplete (lacking detailed results); UNACCEPTABLE, not upgradeable. (J. Wong, 4/1/85).

EPA One-Liner: Positive, but only in B. subtilis strain TKJ6321 without activation of 8 bacterial strains tested; Core Grade = Accepted.

075 037603, "Evaluation of Chevron Naled Technical/Dibrom in the Mouse Somatic Cell Mutation Assay," (Litton, 6/84). Naled technical (92.5%) at dosages of 0, 3, 20 or 150 mg/kg by gavage days 8.5-12.5 of gestation to 120-181 plugged female C57B1/6 mice per group; 34 to 38 litters per group; ethyl nitrosourea (i.p.) used as positive control; decreased lactation index at high dose; no evidence of a positive result in the spot test; UNACCEPTABLE - not a FIFRA guideline study. (J. Wong, 4/1/85 and J. Remsen (Gee), 12/27/86).

EPA One-Liner: Negative for increase in recessive coat color "spot" presumably indicative of mutational events consisting of intragenic base- pair changes, deletions and somatic crossing over. Core Grade = Acceptable.

044 022773. Partial duplicate of (28 pp) 037603 above.

044 022772, "Pilot Evaluation of Chevron Naled Technical in the Mouse Somatic Cell Assay", (Litton, 6/84). NOT REVIEWED.

SBCS31275E: Rebuttal to gene mutation and somatic cell mutation studies in reference to 037603. No new or useful information provided (022772), studies remain UNACCEPTABLE. (F. Martz, 7/28/87).

042 022775, "Mutagenicity of Organophosphorus Compounds in Bacteria and Drosophila" (DNA repair in E. coli, publication in Mutation Research, 28: 405-420, 1975). E. coli (7 strains) tested; also tested with several strains of Salmonella including TA1535; no mutagenicity indicated, but insufficient information for independent assessment; Incomplete (missing protocol information and detailed results); very poor copy; UNACCEPTABLE, not upgradeable. (J. Wong, 3/28/85).

EPA One-Liner did not report on E. coli results.

Summary: Several studies have been conducted in bacteria with mixed results in inadequately reported studies. The previous version of this summary indicated that a guideline study was required to address the conflicting results. This has been done. With the submission of # 072239 in 215-105, with sufficient data to make an evaluation, the collective data indicate that naled is not clearly mutagenic in microbial systems. As noted in the 1-liners, where a notation of a possible effect was made, inadequate data were available for some and equivocal results were reported in others. Gee, 5/23/89.

CHROMOSOMAL ABERRATION

** 074 037601, "Mouse Bone Marrow Micronucleus Assay With Chevron Naled Technical (92.0% Purity, SX-1397)," (Chevron, 11/21/84). Male mice dosed at 55, 110 and 220 mg/kg; female mice dosed at 55, 110 and 290 mg/kg; sacrificed 5 mice/sex/group at 24, 48 and 72 hours; PCE/NCE and micronucleated PCE's showed NO ADVERSE EFFECT. Complete, ACCEPTABLE. (J. (Remsen) Gee, 1/27/86).

No EPA One-Liner available.

050 026893: Partial duplicate of 037601.

** 043 022769, "In Vivo Cytogenetics Study in Rats, Naled Technical (SX-1397)", (EG&G Mason Research Institute, 6/6/83, report MRI-193-CCC-82-82). Naled (no purity information); Sprague-Dawley rats; low-dose (6.17 mg/kg to females; 3.88 mg/kg to males); mid-dose (20.57 mg/kg to females; 12.93 mg/kg to males); and, high-dose (61.7 mg/kg to females; 38.8 mg/kg to males); doses administered in a single oral gavage dose to 4 animals/sex/group/sacrifice interval; rats sacrificed at 6, 24 or 48 hours; NO ADVERSE EFFECT; Complete, ACCEPTABLE. (J. Wong, 3/26/85).

EPA One-Liner: Negative for chromosome aberrations in bone marrow cells at oral doses of 3.88, 12.93 and 38.80 mg/kg to males, and 6.17, 20.57 and 61.70 mg/kg to females. Insufficient dosage to effect target tissue. Core Grade = Unacceptable.

DNA DAMAGE/REPAIR

** 105 072240, "Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocyte Cultures by Autoradiography: Naled Technical", (Sitek Research Laboratories, laboratory study no. 0087-5100, 11/9/88). Naled technical, purity 93.3%, tested with rat hepatocytes at concentrations of 0 (DMSO), 1.0, 2.5, 5.0, 7.5, 10, or 50 µg/ml for 18 hours. Under study conditions, Naled did not induce unscheduled DNA synthesis in rat hepatocytes. ACCEPTABLE. (Kishiyama, 5/22/89 and Gee, 5/24/89))

042 022777, "Activity of Organophosphorus Insecticides in Bacterial Tests for Mutagenicity and DNA Repair - Direct Alkylation Versus Metabolic Activation and Breakdown. II. O,O-Dimethyl-0-(1,2-Dibromo-2,2-Dichloroethyl)-Phosphate and Two 0-Ether Derivatives of Trichlorfon," (Chem.-Biol. Interactions, 43: 361-370, 1983, Braun et al.). Naled (no purity information), 10 or 40 μM/plate; Proteus mirabilis strains PG 713 and PG 273; No adverse effect indicated, but insufficient information provided for independent adverse effects assessment; Incomplete (no detailed protocol or results information); UNACCEPTABLE, not upgradeable. (J. Wong, 3/28/85).

EPA One-Liner: Negative for DNA damage in P. mirabilis; Core Grade = Acceptable.

NEUROTOXICITY

Rangefinding Study:

127 130856 "A Rangefinding Study for A Subchronic Delay Neurotoxicity Study in Laying Hens (Gallus gallus domesticus)," (Beavers, J.B. and Foster, J.W., Wildlife International Ltd., Easton, MD; Project ID #: 263-129, VP-10103, 4/29/94). Naled technical (91.7% pure) was administered by gavage at 0 (0.25% carboxymethyl cellulose), 2, 4, 8, and 16 mg/kg daily for 7 days, followed by a 4 day observation period. NOEL = 2 mg/kg (Clinical signs and decreased locomotor activity at ≥ 4 mg/kg and increased mortality were observed at ≥ 8 mg/kg.) **Possible adverse effects:** Signs of cholinesterase inhibition (≥ 4 mg/kg) and increased mortality occur (≥ 8 mg/kg). **These data are supplemental.** M. Silva, 7/21/94.

Definitive Studies:

** 126 130839 "A 28-Day Subchronic Delayed Neurotoxicity Study in Laying Hens (Gallus gallus domesticus)," (Beavers, J.B. & Foster, J.W., Wildlife International Ltd., Easton, MD; Project ID #: 263-132, VP-10103, 4/29/94). Naled technical (91.7% pure) was administered by gavage to White Leghorn Hens (Gallus gallus domesticus--4/dose for NTE & AChE determinations; 10/dose for behavior/pathology) at 0 (vehicle = 0.25% CMC), 0.5, 2.0 & 4.0 mg/kg and positive control

hens received TOCP at 0 (vehicle = corn oil), 35 or 45 mg/kg for 28 days. Treatment was followed by a 21 day observation period. The NOEL for brain ChE was re-evaluated and decreased, based upon biological relevance of inhibition values. NOEL = 0.5 mg/kg (There was a significant decrease in brain AChE levels at $\geq$ 2.0 mg/kg.) Acceptable. No adverse effect. M. Silva, 1/9/96.

** 108 088863 "Acute Delayed Neurotoxicity Study with Naled Technical in the Domestic Hen," (Redgrave, V., Gopinath, C., Anderson, A., Cameron, D., Rao, R. and Dawe, I., Huntingdon Research Centre, Ltd., England, 7/30/90). Naled technical (Batch NB 10198-41, 98% pure) was used on hybrid brown laying hens at 0 (0.5% sodium carboxymethylcellulose) or 42 mg/kg (40 hens) in a single dose (by gavage), followed by a repeat dose after 21 days in birds showing a negative neurotoxic response. Naled treated birds were protected with atropine sulphate (10 mg/kg) and 2-PAM (50 mg/kg) immediately prior to dosing. A satellite group was maintained for assessing brain ChE and NTE, treated at 0, 8 (5 hens/group) and 42 mg/kg (10 hens) with a single dose and a 24-hour observation period (then sacrifice). TOCP (corn oil) was used as a positive control (500 mg/kg--10 hens in the main group and 5 hens in the satellite). **No adverse effect**. The positive control was functional. **Acceptable.** M. Silva, 1/3/91.

107 087179 This volume contains a letter from Therese St. Peter (State Regulatory Affairs Manager), dated July 18, 1990. The letter contained information about study 088863 and a discussion of the histopathological effects observed and their conclusions regarding possible adverse effects. In addition, a table is included which shows the results of the grading for neurotoxic effects (also in the main report). M. Silva, 1/11/91.

076 037604, "The Evaluation of Dibrom As A Potential Neurotoxic Agent Following Oral Administration to Hens Protected by Atropine Sulfate," (FDRL, 11/14/78). Naled technical (no purity information) at 117 mg/kg in a single gavage dose in atropine-protected hens; NOEL = 117 mg/kg (no delayed neurotoxicity at the only dose tested); UNACCEPTABLE, incomplete, unlikely upgradeable (no repeat dosage given in absence of response to first dose). (C. Aldous, 1/21/86).

No EPA One-Liner available.

SBCS31275E: Rebuttal to neurotoxicity study referenced above. No new or useful information provided, study remains UNACCEPTABLE. (F. Martz, 7/28/87). No record number. CDFA response (letter dated 8/6/87) to rebuttal (Chevron letter dates 11/24/86 and 3/6/87) on hen delayed neurotoxicity study. New Report Status: No change from previous status of unacceptable, but now upgradeable.

034 928895. Partial duplicate of 037604 . (J. Wong, 3/26/85).

045 016194. Partial duplicate (20 pp) of 037604.

143 131952 "A Range-Finding Acute Study of Valent Naled Technical in Rats," (Lamb, I.C., WIL Research Laboratories, Inc., Ashland, OH; Project #: WIL-194006, 2/9/94). Naled technical (92.7% pure) was administered by gavage to Sprague-Dawley Crl:CDBR rats (1-4/sex/dose) at: **Part A:** 0.5, 1, 5, 35, 75, 100, 125 & 150 mg/kg. **Part B:** 300 mg/kg. **Part C:** 600 mg/kg. **Part D:** 50, 450, 500 & 550. **Part E:** 25 & 450 mg/kg (vehicle = 0.5% carboxymethylcellulose). In Part A, post-dosing observation times were 1, 1.5, 2, 3, 4, 5, 6, 7 & 8 hours and Parts B-E observation times were 0.25, 0.5, 0.75, 1, 2 & 3 hours. All animals were observed for a total of 7 days. At 450 mg/kg 1/4 females died on the day of dosing. All animals at ≥ 500 mg/kg died or were killed moribund within 24 hours post-dosing (most within 45 minutes). Animals treated at 0.5-300 mg/kg survived to termination (day 8). Clinical signs showed gait alterations (rocking, lurching, swaying, prostration), whole body tremors, constricted pupils, reduced forelimb/hindlimb grasp, exophthalmus and splayed hindlimbs at ≥ 75 mg/kg, salivation at ≥ 300 mg/kg and hypoactivity at ≥ 450 mg/kg (peak effects at 0.5 hr post-dosing). At ≤ 50 mg/kg, clinical signs were few (gait alterations: rocking, lurching & swaying) were observed at 50 mg/kg (1 male) at 0.5 & 0.75 hr only. Constricted pupils were observed at 0.5, 1, 5 & 35 mg/kg (no dose relationship). Some body weight loss was observed at 450 mg/kg (1 surviving male) & 300 mg/kg (2/2 females). NOEL = 35 mg/kg. These data are supplemental. M. Silva, 11/3/94.

** 122 129873 "An Acute Neurotoxicity Study of Naled Technical in Rats," (Lamb, I.C., WIL Research Laboratories, Inc., Ashland, OH; WIL-194007, Sponsor #: VP-10102, 7/12/93). Naled technical (purity = 92.7%) was administered by gavage to Sprague-Dawley Crl:CD BR rats at 0 (vehicle = 0.5% carboxymethylcellulose), 25, 100 and 400 mg/kg (12/sex/dose at 0, 25 & 100 mg/kg; 16/sex at 400 mg/kg). Animals were observed for 14 days post-treatment.NOAEL = 25 mg/kg (At 400 mg/kg, both sexes showed increased mortality, males showed a transient decrease in body weight gain. Clinical signs were observed in both sexes at 400 mg/kg: orange and/or yellow material on various surfaces and red material around the mouth, nose and/or eyes, gait alterations, tremors and hypoactivtiy (≥ 100 mg/kg, rales & retching). No adverse effects:

Effects were observed in the FOB at ≥ 25 mg/kg: Tremors in limbs, reduced hindlimb resistance (≥ 25 mg/kg) and at ≥ 100 mg/kg: sensorimotor activity, neuromuscular, physiological, autonomic, excitability domains in both sexes. These effects were reversed by day 14 to control values.) Acceptable. M. Silva, 6/27/94.

** 125 130838 "A Subchronic (13-Week) Neurotoxicity Study of Naled Technical in Rats," (Lamb, I.C., WIL Research Laboratories, Inc., Project ID: WIL-194008, VP-10104, 4/28/94). Naled technical (92.7% pure) was administered by gavage to Sprague-Dawley, Crl:CDBR rats (10/sex/dose) at 0 (vehicle = carboxymethyl-cellulose), 0.4, 2.0 and 10.0 mg/kg/day for at least 91 days. NOEL = 2.0 mg/kg (At 10 mg/kg, females showed tremors (forelimb/hindlimb and/or whole body). At 10 mg/kg (males) and at ≥ 2.0 mg/kg (females), there was an increase in hair loss. Males at 10 mg/kg showed a mean urination count that was significantly lower than control.) No adverse effect. M. Silva, 7/21/94.

MISCELLANEOUS

090 no record #, "Three-Week Aerosol Inhalation Toxicology Study of Chevron Naled Technical (SX-1554) in Rats," (Chevron, 12/11/86, subchronic inhalation (824) rat). Naled technical, 90%, at 0, 3.4, 7.2 and 12.1 microgram/L to 10/sex/dose for 6 hours/day, 5 days/week for 3 weeks; nasal lesions occurred at 3.4, 7.2 and 12.1 ug/L; possible adverse effect: corneal and nasal lesions; supplemental data. (H. Green and G. Patterson, 4/27/87).

133 131243 "Thirteen Week Aerosol Inhalation Toxicity Study of Chevron Naled Technical (SX-1665) in Rats," (Griffis, L., Chevron Environmental Health Center, Richmond, CA; SOCAL 2400, 8/26/86). F-344 rats (12/sex/dose) were exposed to naled technical (92.1% pure; SX-1665), generated in aerosol, at 0, 0.2, 1.2 and 6.0 ug/L (6 h/day, 5d/week for 13 weeks). In addition, 10 rats/sex (control and 6.0 ug/L) were held for a 6 week recovery.
Dosing Material: Concentration of naled and BDCA (hydrolysis product) in the chamber, MMAD and GSD of the aerosol were determined. Average naled concentrations: 0, 0.23, 1.29 & 5.8 ug/L. Average BDCA concentrations: 0, 0.18, 0.31 & 0.93 ug/L. Average MMAD at 5.8 ug/L = 2.4 um, at 1.29 & 0.23 ug/L < 0.7 um (most of the naled was in vapor).

Observations: Toxicity was determined by daily clinical observations, weekly body weights and food consumptions, clinical pathologies (end of exposure) and cholinesterase determinations (at 2, 7 & 13 weeks--main group; 12, 15 & 19 weeks--recovery groups), gross necropsy examinations, organ weighs & histopathological examinations. There were no treatment-related mortalities. Females at 6.0 ug/L had a significant increase in food consumption during the 2nd half of the study (no effects on body weight). Increased food consumption was sporadic and usually ≤ 10%. Both sexes showed an increase in clinical signs of cholinesterase inhibition at 6.0 ug/L (salivation, nasal and anogenital discharge, abnormal respiratory sounds). Cholinesterase inhibition was as follows:

1. Mean RBC ChE: Significantly decreased in both sexes at ≥ 1.2 ug/L. It remained low in the recovery animals.
2. Mean Plasma ChE: Significantly decreased in both sexes at ≥ 1.2 ug/L. Male levels remained low throughout the 6 week recovery period, where females were reversed at 3 weeks recovery.
3. Mean Brain ChE: Significantly decreased at 6.0 ug/L in both sexes (some reversal by 6 weeks recovery but still a significant decrease).

Hematology: MCH were both significantly increased at ≥ 1.2 ug/L. Males showed an increased MCV at 6.0 ug/L and female MCV was increased at ≥ 6.0 ug/L. Females showed an increased A:G ratio at 6.0 ug/L.

Organ Weights: Absolute and relative kidney weights were increased in females at 6.0 ug/L.

Histopathology: Nasal pathology was observed in treated animals:

Effect Observed	Naled Concentration (ug/L)							
	Males				Females			
	0	0.2	1.2	6.0	0	0.2	1.2	6.0
Level 1:								
Epithelial Dysplasia	0	0	3	2	0	1	1	3
Epithelial Dystrophy		0	0	0	1		0	0	0	0
Suppurative Exudate		0	3	1	0		0	0	0	0

Epithelial Hyperplasia	0	0	0	1	0	0	0	0
Chronic Rhinitis	0	2	1	1	0	2	3	4
Chronic Inflammation	0	0	0	0	0	0	1	0
Level 2:								
Suppurative Exudate	0	1	0	0	0	0	0	0
Hemmorrhage	0	1	0	0	0	0	1	1
Chronic Rhinitis	0	0	1	0	0	0	0	0
Level 3:								
Hemmorrhage	0	2	1	0	1	1	2	1
Level 4:								
Hemmorrhage	0	4	1	0	1	2	3	1

There were 12/sex/dose examined for histopathology. The report did not note that the nasal effects were treatment-related, however it appears that they occurred almost exclusively in treated animals.

Systemic NOEL < 0.2 ug/L (Increased food consumption, increased MCH, MCV and A:G ratio, increased absolute and relative kidney weights. **Possible adverse effect: There was an increase in nasal pathology at all doses and in both sexes of treated animals.)** ChE NOEL = 0.2 ug/L (RBC and plasma ChE were significantly decreased at $\geq$ 1.2 ug/L and brain ChE was significantly decreased at 6.0 ug/L.) These data are supplemental. M. Silva, 8/17/94